PATENT
Attorney Docket No. 01975.0025

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Rudi BRANDS	)	Group Art Unit: 1651
	)	
Application No.: 09/582,342	)	Examiner: A. Ford
	)	
Filing Date: September 18, 2000	)	Confirmation No. 8325
	)	
For: PREPARATION OF CELLS FOR PRODUCTION OF BIOLOGICALS	)	**VIA EFS-WEB**

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed September 5, 2008, and further to Board Rule 41.37, Appellant presents this brief and submit herewith a fee of $540.00 required under 37 C.F.R. § 41.20(b)(2).

The time period for filing an appeal brief was reset to be one-month from the mailing date of the Notice of Panel Decision from Pre-Appeal Brief Review mailed on November 13, 2008. Accordingly, this Appeal Brief is timely filed with the enclosed Petition and fee for a three month extension of time, extending the due date for response to March 13, 2009.

This Appeal responds to the rejections of claims 39-44 set forth in the final Office Action dated May 7, 2008.

If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to Deposit Account No. 06-0916

TABLE OF CONTENTS

I. Real Party In Interest 4

II. Related Appeals and Interferences 5

III. Status Of Claims 6

IV. Status Of Amendments 7

V. Summary Of Claimed Subject Matter 8

VI. Grounds of Rejection 9

VII. Argument 10

VIII. Conclusion 17

IX. Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii) 18

X. Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix) 20

XI. Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x) 21

I. Real Party In Interest

Solvay Biologicals B.V. is the real party in interest. The assignment is recorded at Reel 021499 and Frame 0264 on September 9, 2008.

II. Related Appeals and Interferences

There are currently no other appeals or interferences, of which Appellant, Appellant's legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Claims 39-44 are pending. Claims 1-38 are canceled. Claims 39-44 stand rejected and are appealed. A complete listing of the pending claims is included in the attached appendix. No claim has been allowed.

IV. Status Of Amendments

No claim amendments have been made in response to or subsequent to the final Office Action dated May 7, 2008.

V. Summary Of Claimed Subject Matter

The present invention is concerned with a method for the preparation of cells for use in the production of biologicals. Appellant's specification, page 1, lines 4-5. In one embodiment, which is recited in **independent claim 39**, the invention relates to a method for the preparation of cells for use in the production of a biological, the method comprising culturing cells to a desired cell volume of a preproduction batch, wherein the cells are anchorage dependent cells, where after in a repeated discontinuous process a) a first part of the cells of the preproduction batch is used for the preparation of at least one production batch, and b) the remaining part of the cells of the preproduction batch is used as a seed for the preparation of at least one subsequent preproduction batch. *Id.* at page 2, lines 1-7 and 20-21.

VI. Grounds of Rejection

Claims 39-44 stand rejected under 35 U.S.C. § 103 over BRYAN GRIFFITHS & DENIS LOOBY, *Scale-Up of Suspension and Anchorage-Dependent Animal Cells, in* 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 59, 59-75 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("Griffiths") in view of "Friendship Cake/Bread History" available at http://recipecircus.com and "Amish Friendship Bread" available at http://en.wikipedia.org.

VII. Argument

A. The Examiner Has Failed to Establish a *Prima Facie* Case of Obviousness over the Cited References.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142. In *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q. 2d 1385 (2007), the Supreme Court confirmed that the "framework for applying the statutory language of §103" was still based on its landmark decision in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Under *Graham*, there are four factors for consideration when determining whether an invention is obvious:

(1) the scope and content of the prior art;

(2) the differences between the prior art and the claims at issue;

(3) the level of ordinary skill in the art; and

(4) secondary considerations.

383 U.S. at 17, 148 U.S.P.Q. at 467. Although the question of obviousness must be resolved on the basis of these factual determinations, the Supreme Court pointed out that there is no inconsistency between the *Graham* analysis and the idea underlying the teaching, suggestion, or motivation ("TSM") test. *KSR*, 127 S. Ct. at 1741, 82 U.S.P.Q. 2d at 1389. Further, the USPTO has solidified that the TSM test is a valid rationale for determining obviousness. *See* M.P.E.P. § 2141.

In the present § 103 rejection, the Examiner is relying on the TSM rationale to support her conclusion of obviousness. *See* final Office Action at pages 5-7. Under this rationale, the Examiner has the burden to at least demonstrate (1) a finding that there is some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (2) a finding that there was a reasonable expectation of success to make the proposed modification. *See* M.P.E.P. § 2143(G). Moreover, to establish a *prima facie* case of obviousness, the Examiner has the burden of establishing that the prior art references teach or suggest all the claim limitations. *See In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Appellant respectfully submits that the Examiner has not met her burden. Thus, the Examiner has failed to establish a *prima facie* case of obviousness over the cited references.

1. The Examiner Has Failed to Establish that the Cited References Teach or Suggest All the Claim Limitations.

At page 5 of the final Office Action the Examiner asserts that Griffiths discloses "splitting and passaging the cells of their 'preproduction batch.'" *See* pages 65-67 and Fig. 4. However, a thorough review of Griffiths reveals no discussion of splitting cells into two parts in the manner claimed. When it comes to growing cells, the cells in Griffiths are always used as a single "part" and are never diverted for more than one purpose.

In addition, the Examiner's handwritten note on page 67 of Griffiths identifies step 6 of the procedure disclosed as a "discontinuous procedure." This is incorrect. The separation of cells from their substrate after a period of growth is not a repeated

discontinuous process which includes "splitting" of anchorage-dependent cells, as defined in Appellant's claimed invention. *See* page 3, lines 12-18 of Appellant's specification. Accordingly, the Examiner has failed to establish that the cited references teach or suggest all the claim limitations.

2. The Examiner failed to Meet her Burden under the TSM rationale.

The primary reference cited in the rejection, Griffiths, discloses protocols for preparing cell cultures. To the contrary, the secondary references, the "Friendship Cake/Bread History" and the "Amish Friendship Bread" articles only disclose a process of preparing bread. Applying the Graham factors, and considering the level of ordinary skill in the area of cell culture protocols, one would not conclude that this level includes the skill of a baker. Therefore, there is no reason why one skilled in that particular art would consider applying techniques used in making bread to a process for preparing cells for the production of a biological, for example, a virus.

Moreover, even though the "Friendship Cake/Bread History" and the "Amish Friendship Bread" articles may disclose dividing up the starter culture into two parts, given that the process of making bread is completely unrelated to cell culture protocols, there is no way one of ordinary skill in the art would have been able to predict the results of using this technique in a scale-up process for the production a biological with any reasonable expectation of success, and without the benefit of hindsight. Thus, the Examiner has failed to meet her burden under the TSM rationale.

3. The Art Teaches Away from the Claimed Invention.

There are technical difficulties, e.g., homogeneity problems, associated with scaling-up anchorage-dependent cells. Indeed, Griffiths even recognizes these difficulties. *See* pages 59-60 and 65-66. Because of these difficulties, other references in the pertinent art, for example WO 97/37000 to Gröner et al. ("Gröner") (submitted with the IDS filed May 7, 2008), teach away from scale-up of anchorage anchorage-dependent (adherent) cells for use in the production of a biological. In particular, at page 3, line 18 to page 4, lines 16, Gröner discusses the problems associated with scaling up of anchorage-dependent cells. To address these problems, the process in Gröner converts anchorage-dependent cells to cells that grow in suspension to enable better scaling up. *See* claim 1, page 4, lines 19-24, page 5, lines 18-26, and Example 1.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is "strong evidence of unobviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 U.S.P.Q. 479, 484 (1984). As discussed above, Gröner discourages scaling-up of anchorage-dependent cell systems for the production of a biological. Considering the drawbacks associated with scaling up anchorage-dependent cells, it would be unlikely for one of ordinary skill in the art to use anchorage-dependent cells when devising a scaled-up preparation of cells for use in the production of biologicals. Thus, the art teaches away from the claimed invention.

In view of the foregoing, Appellant submits that the Examiner has failed to establish that the claimed invention is *prima facie* obvious in view of the cited art.

B. Applicant has Rebutted any *Prima Facie* Case of Obviousness.

1. Applicant's Claimed Method Satisfied a Long-Felt Need.

Even if the Examiner has established a *prima facie* case of obviousness, which she has not, Appellant can come forward with arguments and/or evidence to rebut the *prima facie* case. *See* M.P.E.P. § 2145. Rebuttal evidence may include evidence of "secondary considerations," such as long felt but unsolved needs. *See id.*; *see also Graham v. John Deere Co.*, 383 U.S. at 17, 148 U.S.P.Q. at 467.

The production of biologicals on cell lines requires the preparation of large amounts of cells using a scaling up procedure in bioreactors. Typically, continuous processes are used for scaling up a cell culture population in the context of producing a biological. *See* Appellant's specification at page 3, lines 20-23. First, cells are grown in a first bioreactor, and after a certain cell density is reached, the cells are fed continuously from the first bioreactor into a second bioreactor. *Id.* at lines 24-25. In this second bioreactor, viruses are grown on the cells and subsequently these viruses are withdrawn continuously from this second bioreactor. *Id.* at lines 25-27. Generally, these types of preparation procedures are very time consuming and necessitate the operation of a large number of bioreactors for the preparation of the cells as well as for the production of the biologicals. *See id.* at page 1, lines 29-32. Thus, there has been a long-felt need for a faster and more efficient process.

Appellant has met this need by inventing a new and faster process for scaling up a cell culture for the production of a biological, wherein the cells are anchorage

dependent cells. Unlike continuous scaling up procedures, Appellant's claimed method uses a discontinuous process. *See* Appellant's specification at page 2, lines 1-15. In embodiments of the claimed invention, cells are cultured to produce a preproduction batch, and then the cells of the preproduction batch are divided into two parts. *See id.* at page 2, lines 1-15. The first part, approximately 80-90% of the cells, is used to prepare a culture of cells to grow a biological such as a virus for a vaccine. *Id.* at page 2, lines 4-5 and 27-28. The second part, approximately 10-20% of the preproduction batch, is used as a seed for at least one additional batch not immediately used for the production of any biological product. *See id.* at page 2, lines 6-7 and 30-32. The cells of the second part of the preproduction batch can be expanded to a greater cell population for the preparation of at least one subsequent preproduction batch. *See e.g., id.* at page 6, lines 15-16. Thus, using Appellant's claimed method, a vaccine manufacturer, for example, can rapidly produce vaccine without waiting for all preproduction batches to reach full maturity. *See* Appellant's specification at page 3, line 35 to page 4, line 2.

As discussed above, the Examiner asserts that the claimed repeated discontinuous (splitting) process would have been obvious based on the disclosure in articles titled "Friendship Cake/Bread History" and "Amish Friendship Bread." *See* final Office Action at page 5. However, the fact of the matter is, prior to Appellant's claimed invention no one considered splitting the preproduction batch (starter culture) used in the production of a biological into two parts. Prior to Appellant's claimed invention, cells for use in the production of a biological were only produced using a continuous process in which the entire preproduction batch was used for preparing a biological. As

discussed above, this continuous process was slow and necessitated a number of bioreactors for the preparation of cells as well as for the production of the biological. Recognizing this long-felt need in the industry, Appellant invented a method for the preparation of cells for use in the production of a biological comprising a discontinuous process in which the preproduction batch was divided into two parts: a first part used for the production of a biological and a second part used as a seed for the preparation of at least one subsequent preproduction batch. By splitting the preproduction batch into two parts, Appellant's claimed method provides a faster and more efficient process for scaling up a cell culture for the production of a biological. Thus, Appellant's claimed method satisfied a long-felt, but unsolved need in the industry, which is further evidence that rebuts any *prima facie* case of obviousness based on the cited references.

VIII. Conclusion

For the reasons given above, pending claims 39-44 are allowable and reversal of the Examiner's rejection is respectfully requested.

If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 6, 2009

By: Jennifer Leach
Jennifer R. Leach
Reg. No. 54,257

IX. Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

1-38. (Cancelled).

39. (New) A method for the preparation of cells for use in the production of a biological, the method comprising culturing cells to a desired cell volume of a preproduction batch, wherein the cells are anchorage dependent cells, where after in a repeated discontinuous process:

a) a first part of the cells of the preproduction batch is used for the preparation of at least one production batch, and

b) the remaining part of the cells of the preproduction batch is used as a seed for the preparation of at least one subsequent preproduction batch.

40. (New) The method according to claim 39, wherein in the repeated discontinuous process:

a) the first part of the cells of the preproduction batch is transferred to be used for the preparation of at least one production batch, and

b) the remaining part of the cells of the preproduction batch is transferred to be used as a seed for the preparation of at least one subsequent preproduction batch.

41. (New) The method according to Claim 39, wherein a first preproduction batch is prepared from a working seed stock by at least one passage step.

42. (New) The method according to Claim 39, wherein the anchorage dependent cells are grown on a substrate and released from the substrate prior to each transfer step.

43. (New) The method according to Claim 42, wherein the substrate comprises particulate matter or a solid support.

44. (New) The method according to Claim 39, wherein the cells are for use in the production of virus.

X. Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

No evidence is being relied upon by Appellants in this appeal.

XI. Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

No related proceedings.